Commentary

RESOLVE-ing sepsis in children – not yet!

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Abstract

The Researching Severe Sepsis and Organ Dysfunction in Children: A Global Perspective study of drotrecogin alfa activated versus placebo was the largest study of adjunctive therapy ever performed in children with severe sepsis. Despite this, the study failed to show any significant differences in outcome between the treatment and placebo groups. The results raise questions about how we should perform meaningful clinical trials in relatively rare conditions such as paediatric sepsis, where the easily measurable endpoints (such as death) are infrequent. A radical rethink of the design of such studies is urgently needed.

The efficacy and safety of drotrecogin alfa activated (DrotAA) (recombinant human activated protein C) was assessed in children with severe sepsis in the Researching Severe Sepsis and Organ Dysfunction in Children: A Global Perspective (RESOLVE) study [1]. In this double-blind, randomised, placebo-controlled, multicentre, multinational trial, 477 patients were enrolled at 104 study sites.

Children with severe sepsis were randomly assigned to a 4-day course of DrotAA or placebo. The primary endpoint was a novel score: the composite time to complete organ failure resolution. Secondary endpoints were the all-cause mortality up to 28 days after treatment, and safety. The primary endpoint was derived in an attempt to determine clinically useful endpoints of morbidity, which both clinicians and patients and their families would view as a tangible outcome (including cessation of vasopressor therapy, extubation and cessation of renal replacement therapy). This novel score, however, like many other scores introduced for the purposes of trial design, has been criticised for generating abstract numbers lacking clear clinical applicability, and for being substantially affected by early mortality events and differences in local management protocols for organ dysfunction (for example, ventilator-weaning protocols, use of blood products and removal of renal replacement therapy) resulting from such a widespread participation of recruiting centres [2].

The RESOLVE study failed to find any clear benefit for the use of DrotAA in children with severe sepsis in the study population as a whole, or in any specific subgroup, either previously defined or after post-hoc analysis. The RESOLVE study did, however, produce some important findings. It was the largest study ever performed in children with severe sepsis, and thus helped to define both the natural history of sepsis in children and the incidence of important complications such as sepsis-induced organ failure and bleeding events.

In the RESOLVE study, patients with the most severe coagulation abnormalities appeared to benefit most from DrotAA, suggesting this group of patients may be a valuable population for further study. In addition, intracranial bleeding events were more common with DrotAA than with placebo (five events during infusion, four of which occurred in infants <2 months, versus one event during infusion, respectively), even though overall bleeding events were similar between the treatment and placebo groups. In view of these results, and of the known increased likelihood of bleeding in early infancy, future trials of DrotAA, and probably other anticoagulants, should avoid enrolling patients of this age.

The disappointing results of the RESOLVE study raise important questions about the overall efficacy of DrotAA. In particular, the negative results of the RESOLVE trial bring into question the results of the Recombinant Human Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) study, the first phase III study of DrotAA in adults with severe sepsis or septic shock. The PROWESS trial was the first study of any adjunctive therapy for sepsis to have produced a statistically significant benefit in the study population overall [3].

Knowledge of the mechanisms of action of activated protein C suggests that is likely to extend beyond its well-documented antithrombotic effects. Activated protein C has been shown to have endothelial cell protective effects and to

DrotAA = drotrecogin alfa activated; PROWESS = Recombinant Human Protein C Worldwide Evaluation in Severe Sepsis; RESOLVE = Researching Severe Sepsis and Organ Dysfunction in Children: A Global Perspective.

limit interactions between endothelial cells and neutrophils in sepsis, as well as inhibiting production of inflammatory mediators by monocytes and macrophages. This suggests that activated protein C is likely to have potential as an anti-inflammatory compound as well as an anticoagulant and profibrinolytic, and thus has potential to interrupt the pathophysiological processes occurring in severe sepsis, making it probably beneficial in such patients [4].

Children with severe sepsis remain at significant risk of death without any hope of effective adjunctive therapies on the horizon. The relative rarity of severe paediatric sepsis coupled with its relatively low mortality make meaningful clinical studies difficult or impossible to perform. In addition, pharmaceutical companies are reluctant to address severe sepsis in children due to the difficulties in designing appropriate studies and the huge costs involved with limited prospects of financial return, despite rulings from regulatory authorities stating that all licensed agents should be fully evaluated in children [5].

What is needed is a rethink of paediatric sepsis studies. There are 2,000 children admitted to paediatric intensive care units in the United Kingdom each year with presumed sepsis, with approximately 20% mortality [6]. Intensivists are failing these children due to the lack of well-defined clinical studies. The paediatric intensive care community is developing a coordinated network for collaborative clinical studies [7], but we need to do more. Routine therapies should be standardised according to protocol, thus removing heterogeneity of therapies between centres. Ethical obstacles could be overcome by removing the need for parental consent to administer adjunctive therapies (once safety concerns have been addressed through appropriate clinical studies), with the assumption of therapeutic equivalence – therefore enabling all children with severe sepsis admitted to designated paediatric intensive care units to be enrolled in clinical trials. Standardised therapeutic regimens and study agents can thus be assessed in a logical and sequential pattern determined by the diagnosis of severe sepsis, in a rational scientific manner, much as new therapies for childhood leukaemia have been evaluated.

Children are also less likely than adults to have significant underlying co-morbidity and are a more homogeneous population than are recruited to adult sepsis studies. Children may therefore be a much more suitable population to evaluate newer therapies in a controlled trial setting, to establish proof of principal and then allow extension of studies into adult trial populations, rather than studies in adults preceding studies in children.

Only by a radical rethink of the way we evaluate new therapies in critically ill children will we be able to properly assess experimental treatment modalities, thus allowing children with sepsis at high risk of death to benefit maximally from adjunctive therapies.

Competing interests

SN has been a paid consultant to Eli Lilly. However, Eli Lilly has had no involvement with this publication, financial or other, and the opinions expressed are the author's personal views.

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